

## King's Research Portal

DOI:

[10.1016/j.ijcard.2017.10.126](https://doi.org/10.1016/j.ijcard.2017.10.126)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Webb, J., Draper, J., Rua, T. D. D. O., Yiu, Y., piper, S., Teall, T., Fovargue, L. E., Bolca, E., Jackson, T. A., Claridge, S., Sieniewicz, B., Porter, B. R., McDiarmid, A., Rajani, R., Kapetanakis, S., Rinaldi, C. A., Razavi, R., McDonagh, T. A., & Carr-White, G. (2018). A cost effectiveness study establishing the impact and accuracy of implementing the NICE guidelines lowering plasma NTproBNP threshold in patients with clinically suspected heart failure at our institution. *International Journal of Cardiology*, 257, 131-136.  
<https://doi.org/10.1016/j.ijcard.2017.10.126>

### Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### Take down policy

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

**1 A Cost Effectiveness study establishing the impact and accuracy of implementing the**  
**2 NICE guidelines lowering plasma NTproBNP threshold in Patients with clinically**  
**3 suspected Heart Failure at our Institution**

4 Jessica Webb BMBCh<sup>1,2</sup>, Jane Draper<sup>1</sup>, Tiago Rua<sup>1</sup>, Yee Yiu<sup>1</sup>, Susan Piper MBBS<sup>1,3</sup>, Thomas  
5 Teall MBBS<sup>1</sup>, Lauren Fovargue PhD<sup>2</sup>, Elena Bolca MBBS<sup>1</sup>, Tom Jackson MBBS<sup>1,2</sup>, Simon  
6 Claridge MBBS<sup>1,2</sup>, Ben Sieniewicz MBBS<sup>1,2</sup>, Bradley Porter MBBS<sup>1,2</sup>, Adam McDiarmid  
7 MD<sup>1</sup>, Ronak Rajani MD<sup>1,2</sup>, Stamatis Kapetanakis MBBS<sup>1,2</sup>, Christopher A Rinaldo PhD<sup>1,2</sup>,  
8 Reza Razavi MD<sup>1,2</sup>, Theresa A McDonagh PhD<sup>2,3</sup>, Gerald Carr-White PhD<sup>1,2</sup>

**9 Departments**

10 <sup>1</sup> Department of Cardiology, Guy's and St Thomas' NHS Foundation Trust, London, SE1  
11 7EH. United Kingdom

12 <sup>2</sup> Division of Imaging Sciences and Biomedical Engineering, King's College London, SE1  
13 7EH, United Kingdom

14 <sup>3</sup> Department of Cardiology, King's College Hospital NHS Foundation Trust, London, SE5  
15 9RS

16 All authors takes responsibility for all aspects of the reliability and freedom from bias of the  
17 data presented and their discussed interpretation

**18 Corresponding author contact information**

19 Dr Jessica Webb Division of Imaging Sciences and Biomedical Engineering, 4th floor  
20 Lambeth Wing, King's College London, SE1 7EH, United Kingdom

21 Tel: +44 7970440562

22 Email: Jessica.webb@kcl.ac.uk

## 23 **Funding**

24 The authors have received funding from the EU FP7 for research, technological development  
25 and demonstration under the grant agreement VP2HF (number 611823). The authors also  
26 acknowledge financial support from the Department of Health, via the National Institute for  
27 Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy' s & St  
28 Thomas' NHS Foundation Trust in partnership with King' s College London and King' s  
29 College Hospital NHS Foundation Trust.

## 30 **Conflicts of Interest**

31 The authors have no relevant affiliations or financial involvement with any organization or  
32 entity with a financial interest in or financial conflict with the subject matter or materials  
33 discussed in the manuscript.

## 34 **Abbreviations**

35 HF Heart failure

36 LVEF Left ventricular ejection fraction

37 HFrEF Heart Failure with reduced Ejection Fraction

38 HFmrEF Heart Failure with mid range Ejection Fraction

39 HFpEF Heart Failure with preserved Ejection Fraction

40 NTproBNP N terminal pro-B-type natriuretic peptide

41 NYHA New York Heart Association

42 ESC European Society of Cardiology

43 MCV mean corpuscular volume

44 PCV packed cell volume

45 GFR glomerular filtration rate

46 **Keywords**

47 Heart Failure (HF)

48 NTproBNP

49 Heart Failure with reduced Ejection Fraction (HFrEF)

50 Heart Failure with mid range Ejection Fraction (HFmrEF)

51 Heart Failure with preserved Ejection Fraction (HFpEF)

52 **Word Count** 2970

53

## 54    **Abstract**

### 55    Aims

56    The 2014 National Institute of Clinical Excellence (NICE) guidelines on the management of  
57    acute heart failure recommended using a plasma NT-proBNP threshold of 300pm/ml to assist  
58    in ruling out the diagnosis of heart failure (HF), updating previous guidelines recommending  
59    using a threshold of 400pg/ml. NICE based their recommendations on 6 studies performed in  
60    other countries. This study sought to determine the diagnostic and economic implications of  
61    using these thresholds in a large unselected UK population.

### 62    Methods

63    Patient and clinical demographics were recorded for all consecutive suspected HF patients  
64    over 12 months, as well as clinical outcomes including time to HF hospitalisation and time to  
65    death (follow up 15.8 months).

### 66    Results

67    Of 1995 unselected patients admitted with clinically suspected HF, 1683 (84%) had a  
68    NTproBNP over the current NICE recommended threshold, of which 35% received a final  
69    diagnosis of HF. Lowering the threshold from 400 to 300pg/ml would have involved  
70    screening an additional 61 patients and only would have identified one new patient with HF  
71    (sensitivity 0.985, NPV 0.976, Area under the curve (AUC) at 300pg/ml 0.67; sensitivity  
72    0.983, NPV 0.977, AUC 0.65 at 400pg/ml). The economic implications of lowering the  
73    threshold would have involved additional costs of £42,842.04 (£702.33 per patient screened,  
74    or £ 42,824.04 per new HF patient).

### 75    Conclusion

76    Applying the recent updated NICE guidelines to an unselected real world population  
77    increases the AUC but would have a significant economic impact and only identified one new  
78    patient with heart failure.

79

## Introduction

Evaluating and managing patients with acute dyspnoea remains challenging in the acute setting. Misdiagnosis of heart failure can lead to morbidity, mortality and increased resource utilization. 70% of heart failure costs are due to costs of hospitalisation and in total, heart failure costs in the United Kingdom are estimated to account for 2% of the total National Health Service (NHS) budget<sup>1 2</sup>. Cost effective diagnosis and management of HF is of paramount importance.

Plasma NTproBNP has been shown to be effective as a rule out test<sup>3 4</sup>. In 2012 the European Society of Cardiology updated their guidelines on the diagnosis of acute heart failure recommending an optimal exclusion cut off point for NTproBNP of 300pg/ml<sup>5</sup>. Two years later, this threshold was endorsed by NICE<sup>6</sup>, updating previous guidelines recommending 400pg/ml as a cut off<sup>7</sup>, on the basis of 6 studies performed in Canada<sup>8</sup>, The United States of America<sup>9</sup>, The Netherlands<sup>10</sup>, Switzerland<sup>11 12</sup> and Australia<sup>13</sup>, that demonstrated benefit when comparing the use of peptides against standard care on mortality<sup>9</sup>, length of stay in the Emergency Department<sup>8-10</sup>, subsequent readmissions<sup>8 9 11 12</sup> and costs<sup>8 9 11 12</sup>, Table 1. The latter three studies used the same randomised test data<sup>11-13</sup> and none of the costs or effects analysed were measured in a context directly applicable to a British NHS hospital<sup>14</sup>. None of the trials showed any statistical difference in length of stay for initial hospitalisation, suggesting that the real economic benefit was found in the Emergency Department assessing which patients could be discharged.

We sought to determine the accuracy and economic implications of reducing the threshold of NTproBNP to 300pg/ml in a NHS hospital in a large unselected population of heart failure patients admitted to a Tertiary Hospital in the United Kingdom with a large A and E department.

## Methods

In our hospital we run a NTproBNP led heart failure service where all patients with suspected heart failure have a plasma NT-proBNP requested. A raised result automatically triggers a review by a HF nurse and if appropriate, an echocardiogram and HF consultant review within 48 hours. There are clear local guidelines coupled with regular teaching sessions in both the

A&E department and on the wards, explaining the rationale for the use of peptide testing and that peptide testing in patients with known HF is not recommended. However, despite this, patients with known HF had their NTproBNP tested. The patients who had known HF and had a NTproBNP tested were included in the analysis as we felt it was important not to exclude the cost implications of real life interpretation of current guidelines.

All consecutive patients who had plasma NT-proBNP tested in our institution over one year were included, between 10/09/2014 and 09/09/2015, Figure 1. The list of patients with NTproBNP tested because of suspected heart failure was checked against all heart failure patients from the same time period previously submitted NICOR dataset to ensure that all heart failure patients were identified. Clinically the heart failure team reviewed all patients with plasma NTproBNP >400ng/l and echocardiography was performed by a sonographer in line with current ESC guidelines <sup>15</sup>, unless the patient had been scanned in the 6 months previously or the symptoms and investigations suggested an acute deterioration recently. Diagnoses were adjudicated through the heart failure multidisciplinary team. When patients were admitted more than once, their first chronological presentation was recorded. Data was collected as part of our Institution's approved Clinical Audit.

#### Assumptions in patients with NTproBNP 300-399pg/ml

For this study, all patients with values between 0 and 399ng/l were also investigated using hospital databases and records to confirm diagnoses, patient demographics, risk factors, length of stay and time to heart failure hospitalisation. Diagnoses were adjudicated through the heart failure multidisciplinary team.

It was noted that 6% of the patients with NTproBNP 400-499pg/ml did not have echocardiography performed within 48 hours, and it was assumed that the same proportion of patients in the NTproBNP 300-399pg/ml cohort would have the same. For this reason, only 57 additional echo were included in the costs analysis. This parameter was subjected to one-way deterministic analyses and exhibited little impact around the overall cost implications.

For estimated length of stay (LOS), the one new patient who would have been diagnosed with heart failure if the NTproBNP threshold was reduced to 300pg/ml was assumed to have had the same length of stay as those patients with a new diagnosis of HF with NTproBNP 400-

499pg/ml. This was based on the median LOS for patients with HF and NTproBNP 400-499pg/ml of 6 days compared to 5 days for the patients without HF and NTproBNP 400-499pg/ml.

Moreover, it was assumed that diagnosing HF in the NTproBNP 300-399pg/ml cohort would alter subsequent readmission rates as patients with a new diagnosis of HF would be started on medical therapy with access to the HF team and education. Originally the plan had been to use readmission rates from published literature, assuming that if the threshold was lowered to 300pg/ml, it could be inferred from the IMPROVE-CHF trial <sup>8</sup> that the readmission rate would be 13%, and if the threshold was kept at 400pg/ml then the readmission rate for patients with BNP 300-399pg/ml would be comparable to the study's 'usual care group' cohort with a 20% rate of readmission for the NTproBNP group and 20% for the control group. However, this trial (and the others referenced in the recent NICE guidelines) used different NTproBNP cut offs, two trials used the cut offs from the PRIDE study <sup>3</sup> 900pg/ml <sup>9</sup> (and possibly 450pg/ml for the small number of patients under 50 years of age <sup>8</sup>) and the other trial 1017pg/ml <sup>10</sup>. As the data published was not comparable to our dataset, it was decided to use the patients with NTproBNP 400-499pg/ml as our reference cohort and assumed that the same rate of rehospitalisation would apply to patients without HF but with NTproBNP of 300-399pg/ml. Over the 15.8 months (range 14.1-27.0), the rate of subsequent HF hospitalisation was 47.1% for patients with HF and NTproBNP 400-499pg/ml, compared to 57.6% with no HF and NTproBNP between 400-499pg/ml. This assumption was also used in the patients with NTproBNP 300-399pg/ml.

#### NT-proBNP Assays

NT-proBNP analysis was performed with the commercially available immunoassay using the Elecsys 1010, 2010, or E170 proBNP assay (Roche Diagnostics GmbH, Mannheim, Germany). Details of the assays, cross-reactivity and coefficients of variation, have previously been reported <sup>3 16</sup>.

#### Cost and cost-effectiveness analyses

The present cost analysis considers all heart failure related costs from an NHS and personal social services perspective. Wherever possible, NHS reference costs are used. With regards to



human resource costs, the hourly cost of the heart failure team was sourced from Personal Social Services Research Unit compendium<sup>17</sup>. If unavailable, internal costs from our Tertiary Hospital in the United Kingdom are considered. The total costs were calculated by multiplying the frequencies by the respective unit cost. Cost-effectiveness analysis evaluates the cost per additional patient correctly diagnosed with heart failure.

The cost of the NTproBNP sample at our institution was £32.64<sup>18</sup>. The length of stay was recorded from hospital records and the cost of theoretical additional length of stay was based on information from the NHS reference Costs<sup>19</sup>. The assumption from NICE was that patients stay an additional two days if they are falsely assessed as being likely or unlikely to have heart failure<sup>6</sup>. The cost of the Heart Failure team was assumed to be an hour of time from a Band 7 clinical nurse (£53/hour)<sup>17</sup>. No additional costs for other members of the heart failure team (consultant, dietician, pharmacist, junior doctors) were included for the patients without heart failure as it was assumed that the rest of the team would only review if a diagnosis of heart failure was made. With regards to patients with diagnosed Heart Failure, a cost of £334.00 was estimated, based on an average of 20 minutes per patient discussed and the presence of one consultant, one registrar and one nurse<sup>17</sup>. The cost of an echocardiogram was £66<sup>17</sup>.

#### Statistical analysis

Data is given as mean  $\pm$  standard deviation (SD) when normally distributed, as median and interquartile range (Q1-Q3) for plasma NTproBNP and other data not normally distributed or skewed, and as frequencies and percentages for categorical variables. The primary endpoints were final diagnosis, length of stay and time to rehospitalisation. Associations between baseline variables were evaluated using 1 way analysis of variance, Mann-Whitney U, T-test and chi-square tests, where appropriate. The accuracy of using NTproBNP to detect HF was assessed using area under the curves, calculated using Prism with the optimal cut off defined as 90% sensitivity. Statistical significance was defined as a p value of <0.05.

## Results

In total, 1995 patients with clinically suspected heart failure had NTproBNP tested of which 20.7% had a final diagnosis of HF. 84% of these patients had a NTproBNP over the current

NICE recommended threshold for ruling out heart failure, of which 24% were diagnosed with HF (1683 had NTproBNP >400pg/ml (84.3%), 61 had NTproBNP between 300-400pg/ml (3.1%), and 251 had NTproBNP <300pg/ml (12.6%). In total, 413 new cases of acute HF were diagnosed (mean age  $72.3 \pm 14.8$  years, 57% male) with 47.9% Heart Failure with reduced Ejection Fraction (HFrEF), 22.0% Heart Failure with mid range Ejection Fraction (HFmrEF), 21.8% Heart Failure with preserved Ejection Fraction (HFpEF) and 8.2% right ventricular systolic dysfunction (RVSD). Only one of the 61 patients with NTproBNP between 300-399pg/ml, was diagnosed with HF.

Despite clear guidance and regular education, 284 patients with known HF had NTproBNP tested on admission.

At 300pg/ml the sensitivity was 0.985, specificity was 0.153 with a negative predictive value (NPV) of 0.976 and positive predictive value (PPV) of 0.233. The area under the curve (AUC) was 0.67 (95% CI 0.64-0.70) and optimal cut off 837.5pg/ml. Using a threshold of 400pg/ml, sensitivity was 0.983, specificity was 0.188, NPV 0.977 and PPV 0.240. The AUC was 0.65 (95% CI 0.62-0.68) and optimal cut off 857.0pg/mL. The difference in AUC was not significant ( $p=0.47$ ). The theoretical number of patients not identified by increasing NTproBNP thresholds is shown in Figure 2. This illustrates that the lower NTproBNP are recorded in patients with HFpEF and RVSD. For all new HF patients, the AUC was calculated to be 0.73 (95% CI 0.70-0.75) with 786pg/ml as the optimal cut off.

The economic implications of theoretically lowering the threshold to 300pg/ml would have cost £90,821.08 compared to the current clinical model, with a NTproBNP threshold of 400pg/ml, that costs £47,979.04, Table 2. One way deterministic sensitivity analyses were performed to the proportion of patients that underwent an echocardiogram, varying from the baseline (57 additional echocardiograms performed) to the minimum (only half of patients, i.e. 30 additional echocardiograms) and maximum (61 additional echocardiograms, i.e. every patient). These changes have little impact in the overall cost implications. The baseline total cost difference per patient screened (£690.67) marginally decreases and increases in the minimum (£661.46) and maximum scenarios (£695.00), respectively. As the cost implications were small, we continued the assumption of 57 echocardiograms, which equated to a difference of £42,842.04 or £702.33 per patient screened. With regards to the cost-

effectiveness analysis, a total cost of £42,842.04 per additional patient identified with heart failure is estimated.

## **Discussions**

The recent updated NICE guidelines to lower the plasma NT-proBNP threshold of 300ng/litre to rule out the diagnosis of heart failure increased the AUC and would have had a significant impact on the heart failure team and costings, with only 1 new patient with HF identified. The additional costs are £42,842.04 over the year, £702.33 per patient screened and in terms of cost effectiveness, for one new HF patient identified £42,842.04/patient. Of the 1995 unselected patients assessed with clinically suspected heart failure 20.7% had a final diagnosis of HF made.

Our study is the first to demonstrate the accuracy and economic implications and diagnostic implications of lowering the threshold of NTproBNP in a real life unselected clinical scenario in the United Kingdom. The NICE recommendations were based on 6 studies (Table 1) that demonstrated cost savings using peptides against standard clinical care that were not based in the United Kingdom with much higher cut offs for NTproBNP than are used clinically in our practice. IMPROVE-CHF<sup>8</sup> and the study performed by Siebert et al<sup>9</sup>, used 900pg/ml, the same cut off as the PRIDE study<sup>3</sup> (and possibly 450pg/ml for the small number of patients under 50 years of age in IMPROVE-CHF) and Rutten et al, used 1017pg/ml<sup>10</sup>. The reduction in costs were largely explained by a reduction of time in the Emergency Department and a reduction of echocardiography required for patients with NTproBNP under their defined threshold. Despite significant advances in our understanding of introducing peptides to clinical care, none of these studies addressed the issue of the economical implications of lowering the threshold as this was not their study objective. Moreover, the trial practice was not in line with the recent recommendations to increase access to echocardiography for patients with a suspicion of heart failure and raised peptides within 48 hours (infact one trial explicitly stated the opposite, that echocardiography was not performed if the NTproBNP elevated and diagnosis presumed to be heart failure). Furthermore, three of the trials (that used the same clinical dataset) found more heart failure patients diagnosed in the standard clinical care cohort. Another issue with these studies was the short length of follow up, with studies being conducted for 30 days, 60 days, 120 days or at longest 360 days. Only one study in Swedish has been published considering the economic implications of lowering the

NTproBNP threshold from 400 to 300pg/ml in 14,346 patients <sup>20</sup>. However the clinical questions addressed was whether it was cost effective to test NTproBNP before echocardiography, and not what other cost implications there would be with changing the threshold. Patients were identified from the central laboratory and costs of the blood tests and echocardiography were retrieved from the official fee schedule of one of the Swedish regions. They found that with a strict sequential testing strategy that there could be substantial cost reductions, with a major saving seen in younger patients. The authors found that costs were reduced by more using 400pg/ml as the cut-off (33-36% reduction when 400pg/ml the threshold compared to 28-29% with 300pg/ml).

One of the striking findings of our study was the overall poor adherence to the guidelines in real life practice. We estimate that £9269.76 could have been saved if patients with known heart failure did not have NTproBNP checked. Despite evidence that NTproBNP can be used to predict prognosis, in our hospital the Seattle heart failure score is used that does not depend on NTproBNP results <sup>21</sup> and so NTproBNP is not currently indicated in our institution in patients with known HF. Moreover, the trials references by NICE were designed to test natriuretic peptides in the Emergency department, whereas in this real life practice, 25% of the patients presenting with acute heart failure were actually diagnosed on the hospital wards, Figure 1. The 2014 NICE guidelines <sup>6</sup> suggest that of the patients not identified initially with acute heart failure, 80% will be identified during their admission and the remaining 20% will have a higher readmission rate over the following three months. The pressures on the four hour A&E waiting times, the number of acute medical beds as well as changes in the structure of the medical take may all contribute to over a quarter of the acute patients identified on the medical wards. Furthermore, there were 1298 patients who were suspected of having HF and had NTproBNP tested, but were found not to have HF. Although this number initially appears high, this represents only 0.7% of the total proportion of patients presenting to our Accident and Emergency (A&E), given that 182,720 adults were seen with 26,779 medical inpatient admissions at our institution over the same time scale <sup>22</sup>. There are two points that should be highlighted, first, is the number of patients with suspected HF but who are diagnosed with another condition appropriate or could this be reduced, and second, is the number of patients being seen in A&E, and being admitted in our institution, in line with previously published literature. Addressing the first point, the number patients with elevated NTproBNP but without HF are possibly elevated as in our institution, a raised NTproBNP

results in an automatic referral to the HF team. There has been considerable progress made recently through education events in both the medical and A&E departments to implement and explain the rationale for guidelines and NTproBNP testing, and to prevent unnecessary testing (of note, the cost of testing NTproBNP in patients without HF was £42,366.72). It is important to emphasize that our results reflect our real life experience of using NTproBNP. The second point is that the number of patients admitted with HF is lower than the 5% all emergency hospital admissions reported in the 2010 NICE guidelines <sup>7</sup>, that was based on two publications from 2002. Indeed, it is lower than recent Accident and Emergency Statistics that suggest cardiorespiratory conditions were the 6<sup>th</sup> and 7<sup>th</sup> most common reason for an emergency presentation in the United Kingdom <sup>23</sup>. More work is needed to understand this further, and whether the populations are comparable.

The patients were not separated into those tested immediately in A&E and those tested on the medical wards as we found that patients were moved through to the wards quickly. Of the patients with NTproBNP 300-399pg/ml, only three were tested on the medical wards once their initial diagnosis had been disproved.

The strengths of the study are that all patients were included who had NTproBNP tested and so the analysis represents real life practice. In addition, the costs and infrastructure are comparable to other UK hospitals. From an economic point, the modelling was based on the costs of tests, staff time and length of stay in line with the NICE suggestion that an elevated NTproBNP resulted in additional length of stay irrespective of the final diagnosis. We have not taken into account the economic or health benefits of early diagnosis and would need to address this prospectively. Weaknesses of the study are that our population included all patients clinically suspected of having HF from both the A&E/acute admission units and also the hospital wards, although this was only 3 patients in the NTproBNP300-399pg/ml category.. Even though this is not directly equivalent to studies published, the economic implications of lowering the threshold are still applicable. In addition, our study compared real-life practice with guideline directed practice, which will often vary. Patients who presented to other hospitals with HF readmissions were not included in the analysis. The inherent variability of NTproBNP was not directly considered, which is relevant when the reference change value has been shown to be 70.7% in health volunteers and 61.7% in patients with HF <sup>24</sup>, with increased accuracy seen in Asian patients <sup>25</sup>. Moreover, our hospital

run a NTproBNP led HF service which is not necessarily comparable to other NHS hospitals, as it may have resulted in additional patients having NTproBNP tested. Despite these important limitations, our results are important as they demonstrate the additional costs of lowering the NTproBNP threshold in our institution with only 1 additional patient with HF being identified.

Competing interests:

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years ; no other relationships or activities that could appear to have influenced the submitted work.”

The study was approved through the Hospital’s clinical audit department. Our study complies with the Declaration of Helsinki

This work was supported by the EU FP7 for research, technological development and demonstration under the grant agreement VP2HF (number 611823). The authors also acknowledge financial support from the Department of Health, via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy’ s & St Thomas’ NHS Foundation Trust in partnership with King’ s College London and King’ s College Hospital NHS Foundation Trust.

The researchers were independent from their funders when conducting this study.

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

345 The lead author, Jessica Webb, affirms that the manuscript is an honest, accurate, and  
346 transparent account of the study being reported; that no important aspects of the study have  
347 been omitted; and that any discrepancies from the study as planned (and, if relevant,  
348 registered) have been explained.

349 Data sharing: no additional data available.

## References

1. Stewart S, Horowitz JD. Home-based intervention in congestive heart failure: long-term implications on readmission and survival. *Circulation* 2002;**105**(24):2861-6.
2. Petersen S RM, Wolstenholme J. Coronary heart disease statistics: heart failure supplement. London: British Heart Foundation. Available from [www.heartstats.org/datapage.asp?id=1574](http://www.heartstats.org/datapage.asp?id=1574) [accessed July 2010] 2002.
3. Januzzi JL, Jr., Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *The American journal of cardiology* 2005;**95**(8):948-54.
4. Thygesen K, Mair J, Mueller C, et al. Recommendations for the use of natriuretic peptides in acute cardiac care: a position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. *European heart journal* 2012;**33**(16):2001-6.
5. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European journal of heart failure* 2012;**14**(8):803-69.
6. NICE. Acute heart failure: diagnosing and managing acute heart failure in adults. Commissioned by the National Institute for Health and Care Excellence. 2014;**Clinical guideline 187**.
7. NICE. Chronic heart failure: the management of adults with chronic heart failure in primary and secondary care (Partial update) National Institute for Clinical Excellence. 2010.
8. Moe GW, Howlett J, Januzzi JL, et al. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation* 2007;**115**(24):3103-10.
9. Siebert U, Januzzi JL, Jr., Beinfeld MT, et al. Cost-effectiveness of using N-terminal pro-brain natriuretic peptide to guide the diagnostic assessment and management of dyspneic patients in the emergency department. *The American journal of cardiology* 2006;**98**(6):800-5.
10. Rutten JH, Steyerberg EW, Boomsma F, et al. N-terminal pro-brain natriuretic peptide testing in the emergency department: beneficial effects on hospitalization, costs, and outcome. *American heart journal* 2008;**156**(1):71-7.



11. Mueller C, Laule-Kilian K, Schindler C, et al. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. Archives of internal medicine 2006;**166**(10):1081-7.
12. Breidhardt T, Laule K, Strohmeyer AH, et al. Medical and economic long-term effects of B-type natriuretic peptide testing in patients with acute dyspnea. Clin Chem 2007;**53**(8):1415-22.
13. (AHTA) AHTA. Adelaide Health Technology Assessment. B-type natriuretic peptide assays in the diagnosis of heart failure. Part A: in the hospital emergency setting. Part B: in the non-hospital setting. Available from: [http://www.msac.gov.au/internet/msac/publishingnsf/Content/2CDBC3816FDE8D20CA2575AD0082FD8E/\\$File/1087 - Carbon-labelled urea breath tests Report.pdf](http://www.msac.gov.au/internet/msac/publishingnsf/Content/2CDBC3816FDE8D20CA2575AD0082FD8E/$File/1087_-_Carbon-labelled_urea_breath_tests_Report.pdf) 2007.
14. Kind P, Lafata JE, Matuszewski K, et al. The use of QALYs in clinical and patient decision-making: issues and prospects. Value Health 2009;**12 Suppl 1**:S27-30.
15. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal 2016;**Aug**;**18**(8):891-975.
16. Jernberg T, Stridsberg M, Venge P, et al. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. J Am Coll Cardiol 2002;**40**(3):437-45.
17. Curtis LB, A. Unit Costs of Health & Social Care 2016. Personal Social Services Research Unit (PSSRU) 2016.
18. GSTT. Cost of NTproBNP at Guys and St Thomas' NHS Foundation Trust. 2017.
19. Costs NR. National schedule for reference costs: the main schedule. 2015/2016.
20. Ferrandis MJ, Ryden I, Lindahl TL, et al. Ruling out cardiac failure: cost-benefit analysis of a sequential testing strategy with NT-proBNP before echocardiography. Ups J Med Sci 2013;**118**(2):75-9.
21. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;**113**(11):1424-33.
22. Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, Quality Report. Care Quality Commission 24th March 2016.
23. Baker C. House of Commons Library. Accident and Emergency Statistics: Demand, Performance and Pressure. 21 February 2017.

24. Meijers WC, van der Velde AR, Muller Kobold AC, et al. Variability of biomarkers in patients with chronic heart failure and healthy controls. *European journal of heart failure* 2017;**19**(3):357-65.
25. Ibrahim I, Kuan WS, Frampton C, et al. Superior performance of N-terminal pro brain natriuretic peptide for diagnosis of acute decompensated heart failure in an Asian compared with a Western setting. *European journal of heart failure* 2017;**19**(2):209-17.

## Legends

Figure 1: Number of patients diagnosed with Heart Failure in A&E/acute admissions and Hospital wards

Figure 2: Percentage of patients not identified with Heart Failure using different thresholds NTproBNP

Table 1: Published Literature reference in updated NICE guidelines assessing economic implications of lowering the threshold for NTproBNP in the assessment of acute heart failure

Table 2: Economic costings for two NTproBNP models

**Table 1: Published Literature reference in updated NICE guidelines assessing economic implications of lowering the threshold for NTproBNP in the assessment of acute heart failure**

Authors	Peptide	Clinical Environment	Follow up	Patients	Costs based on	Findings	Issues when comparing to our NHS model
Siebert et al, 2006 (8)	NTproBNP	Emergency Department (ED) – prospective, not randomised	60 days	599 patients presenting with dyspnoea	Massachusetts General Hospital accounting database	-NT proBNP model was more effective and less costly than standard clinical assessment -1.6% relative reduction of serious adverse event risk (from 25.8% to 25.4%) -9.4% reduction in costs (savings \$474/patient) compared to standard care: reduce echocardiography by 58%, prevent 13% hospitalisations, reduce LOS by 12% -1% relative reduction in post discharge mortality	-Used >900pg/ml as NTproBNP cut off following results from PRIDE -No echocardiograms performed below NTproBNP cut off or if NTproBNP elevated and primary diagnosis thought to be CHF (not PE). This is fundamentally different to our current practice -Costs very different to UK: echo costed as \$247 compared to £65.70
Rutten et al, 2006 (9)	NTproBNP	Emergency Department (ED) – prospective, not randomised	30 days	477 patients with acute dyspnoea	Erasmus Medical College, Rotterdam, the Netherlands	-Reduction in median overall time to discharge from 3.4 (IQR 0.6-11) days with standard care to 1.9 days (IQR 0.12-8.4) with NTproBNP: No difference in duration of hospitalisation for 62/67% of patients admitted -Trend to reduction in costs \$1364/patient (95%CI -246-3215) -No difference in 30 day mortality	-Rule out HF <93 (males), <144 (females) pg/ml; Ruling in HF > 1017pg/ml -Reduction in cost explained by difference in hospitalisation rate -Median LOS only reduced when factored in approximately 1/3 of patients who were not admitted
Moe et al, IMPROVE CHF, 2007 (7)	NT proBNP	7 Emergency Departments	60 days	500 patients with dyspnoea	Canadian Institute of Health Information costing methodology	-Reduction in median duration of ED visit from 6.3 (4.3-8.6) to 5.6 (4-8) with NTproBNP -Reduction in patients rehospitalised by 60 days from 20% to 13% -Reduction in costs from US \$6129 to US \$5180	- Used NTproBNP cut off from PRIDE but not clarified if >450pg/ml was used for patients <50 years old (although mean age 70, SD 15 and range 20-96 so small number of patients) -No decision analytic framework analyses
Mueller et al, 2006 (10)	BNP	Emergency Department, randomized controlled single blind trial	180 days	452 patients with acute dyspnoea, man age 71 years, 42% female	Costs standardised to according to the actual rates for patients with general insurance who were living in Basel	-Reduction in initial hospital admission rate -Reduction in use of ITU -Reduction in median total days in the hospital at 180 days (10 days (2-24) with BNP, 14 days (6-27 with standard care) -Reduction in total cost	-BNP <100pg/ml rule out, rule in if > 500pg/ml -More patients in the control group were diagnosed with HF than in the BNP group (51% v 45%) and COPD more common in BNP group than in controls (23% v 11%) -Reasons for improved LOS and economic outcome in BNP group, as same number of HF patients. Is it that patients without HF in BNP group are better identified and given alternative treated as they have low BNP
Breidhardt et al, 2007 (11)			Mortality at 720 days, morbidity and economic data at 360 days			-No effect on mortality at 720 days -Differences in length of stay and economic outcome improved in BNP group, with no change in NYHA status.	
AHTA (Adelaide Health Technology Assessment), 2007 (12)			180 days		Population considered to be similar and costs considered to be applicable to Australian Healthcare	-Cost savings for 100 patients = A\$ 33,849 (95% CI A\$ 304-A\$ 67,393) -Cost savings on A\$ 338 per patients presenting to ED with acute dyspnoea	

Table 2: Economic costings for two NTproBNP models

Model screening patients with BNP 300-399 pg/ml	Number of patients	Cost (£) per Intervention	Comments	
Cost of Plasma NTproBNP blood tests	61	£32.64	£1,991.04	
Heart Failure Team initial reviews	61	£53.00	£3,233.00	One hour assumed (£53 cost assumed)
Number of additional echocardiograms performed	57	£66.00	£3,762.00	
Additional length of stay	55	£604.00	£33,220.00	2 extra LOS days (costed at £302/day)
Heart Failure Team Management for 1 new patient	1	£334.00	£334.00	Hourly cost of consultant, registrar and nurse are, respectively: £104; £71 and £53 (assumed 20 minutes/patient).
Change in stay for patient correctly identified as having HF (Median LOS for HF patients 6 days, IQR 1-14)	1	£302.00	£302.00	1 extra day (costed at £302/day)
Readmissions for 1 HF patient (assume LOS 6 days)	0.5	£302.00	£142.24	Assumed that 47.1% of 1 patients will be readmitted and stay for extra 6 days (costed £302/day)
Readmissions for not HF patients (assume LOS 5 days)	31.7	£1,510.00	£47,836.80	Assumed that 57.6% of 55 patients will stay for extra 5 days (costed £302/day)
<b>TOTAL</b>		<b>£</b>	<b>90,821.08</b>	
Model screening patients with BNP > 400pg/ml (not screening patients with BNP 300-399pg/ml)	Number of patients	Cost (£) per Intervention	Total Costs (£)	Comments
Readmissions for 55 patients with NTproBNP 300-399 and not HF (assuming LOS 5 days)	31.7	£1,510.00	£47,836.80	Assumed that 57.6% of 55 patients will stay for extra 5 days (costed £302/day)
Readmissions for 1 patients with NTproBNP 300-399 and HF (assuming LOS 6 days)	0.5	£302.00	£142.24	
<b>TOTAL</b>	<b>£</b>		<b>47,979.04</b>	
<b>OVERALL TOTAL DIFFERENCE</b>	<b>£</b>		<b>42,842.04</b>	
<b>OVERALL TOTAL DIFFERENCE PER PATIENT SCREENED</b>	<b>£</b>		<b>702.33</b>	

